

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

MEHLHORN, Rolf Joachim

Serial No.: 10/759,222

Filed: 20 January 2004

For: METHOD FOR LOADING LIPID
LIKE VESICLES WITH DRUGS
OR OTHER CHEMICALS

Group Art Unit: 1614

Examiner: Kevin E. Weddington

Confirmation No.: 6448

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REHEARING

Dear Sir:

In response to the Board's affirmation of the examiner's rejection of the above-identified application, appellants respectfully request rehearing based on the following considerations.

Appellant would first like to note that it is not appellant's position at this time that the novelty and non-obviousness of the instant invention lies simply in the loading of drugs into vesicles, as exemplified by liposomes, using pH gradients. The examiner has shown well that in general such techniques were known at the time the present application was filed. Novelty and non-obviousness is, however, predicated on appellant surprising finding that, using the method of the instant invention, in particular use if a vesicle/buffer combination in which the vesicle is impermeable to the buffer, that a drug may be maintained within a vesicle for a substantial period of time after the pH

gradient used to load the vesicle has been destroyed. This is an important discovery in that the use of such vesicles for the delivery of drugs involves the insertion of the vesicles into a patient's system where the physiological pH is essentially neutral, 7.0 to 7.2, which necessarily results in the elimination of any pH gradient that had been established to load the vesicle. The Board, however, relying on the unsupported assertion that such characteristic of a vesicle is inherent, or in the Board's words, a "latent property" of vesicles, has placed the burden on appellant to establish that appellant's discovery is an unexpected and surprising development. Appellant respectfully disagrees with the Board's position.

It seems to appellant that before the Board should place the burden of proof on appellant, it is incumbent on the Board to first establish the verity of its position that it is a latent property of a vesicle to maintain a concentration of material loaded into it by means of a pH gradient once the gradient is removed. There certainly is nothing whatsoever in the references cited by the examiner to support the Board's – and presumably the examiner's – position. In the first place, while not expressly stating that the maintenance of a concentration of material after a gradient has been depleted, appellant makes the statement in paragraph 42:

It is clear from the data in Table I that when the intradialysis concentration of probes examined at the end of the incubation period, the vesicles that had been loaded with the pH gradient had retained a such (sic, much) higher concentration of acid that those without a pH gradient. **This example also indicates that it is unnecessary to maintain the pH gradient subsequent to the chemical loading procedure.** (Emphasis added.)

The above is in stark contrast to what Nichols, Deamer and Cramer teach, to the extent that they teach anything actually related to the instant invention. To wit, Nichols expressly states that

When the gradients were destroyed by ammonium chloride additions, the accumulated catecholamines were released, demonstrating that the uptake was reversible and dependent on pH gradients. Nichols, page 271, first full paragraph.

For its part, Deamer's *raison d'etre* is to offer liposomes as a model membrane system in which controlled pH gradients may be established (Deamer, Page 323, Summary). Deamer showed that the quenching of atebrin or 9-aminoacridine was quenched by the inward movement of the fluorescent material into liposomes as the result of a pH gradient. Deamer states, however, on page 326, first full paragraph, that

At higher lipid concentrations, the enhancement may be 250%. Triton (0.1 mM) or **NH₄Cl [ammonium chloride, the same material used by Nichols to destroy the pH gradient] completely reversed the enhancement.**
(Emphasis added.)

The above is amenable to only one reasonable interpretation: that the fluorescent substance was expelled from the liposomes upon destruction of the pH gradient, the opposite of what is claimed in the instant invention.

Finally, Cramer is directed solely to the study of the effect of pH gradient on the transport of carboxylic acids across single bi-layer vesicle membranes. (Cramer, Summary page 295). Cramer offers not a single comment regarding what happens when the gradient is eliminated. Cramer has no bearing whatsoever on the instant invention.

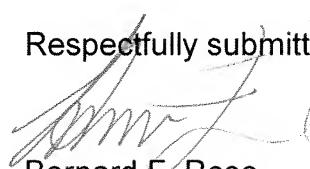
Clearly, there is an utter lack of any statement, however vague, ancillary or tangential, in the references relied on by the examiner to support rejection of the instant application and, apparently, by the Board in making the pronouncement that the delayed release of a substance from a vesicle upon destruction of the pH gradient used to load the material into the vesicle is a latent property of vesicles. In fact, to the extent that any of the cited articles reference eliminating the pH gradient at all, they uniformly note that the disproportionate concentration of the material in the vesicle due to the pH gradient rapidly disintegrates as the material rapidly exits the vesicle. Thus, there appears to be no support for the position that maintenance of a concentration gradient in a vesicle as required by the instant invention is an inherent or latent property of vesicles - in fact, quite the opposite is suggested by the cited references, therefore, appellant should not be required to prove further that his invention is an unexpected and surprising discovery.

Based on the above, it is respectfully requested that the Board reconsider and reverse its decision of affirmation of the rejection of the instant application and instead order it be passed to issue.

Date: 18 March 2011

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Respectfully submitted,



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